REMARKS

The Official Action of May 30, 2000, has been carefully considered and reconsideration of the application as amended is respectfully requested.

Claims 12 and 13 have been amended to remove the basis for the rejection under 35 USC 112, second paragraph. All claims as amended are believed to be sufficiently definite to satisfy the dictates of 35 USC 112, second paragraph.

The Examiner has maintained the rejection under 35 USC 103(b) as allegedly being unpatentable over Andersag. Applicants respectfully traverse this rejection.

In maintaining the rejection, the Examiner contends that the claimed method is obvious in the absence of unexpected results. While Applicants believe that the evidence presented in the specification is sufficient to establish unexpected results (see discussion below), they also respectfully call the Examiner's attention to MPEP Section 716.01(a) which recognizes that the Examiner must consider other objective evidence of nonobviousness (in addition to evidence of unexpected results) in determining patentability. In particular, the Examiner must consider evidence that shows a long-felt need to solve the problem solved by the claimed invention (see MPEP Sections 716.01(a) and 716.04).

In the present case, the evidence of record in the specification and in literature references cited of record establish a long-felt need for a primaquine derivative that has enhanced anti-

malarial activity and yet overcomes the longstanding problem posed by the toxicity of primaquine. This problem is described in the specification of the present application at, for example, the paragraph bridging pages 2 and 3 of the specification. Moreover, Applicants respectfully call the Examiner's attention to the Saxena et al article cited in the Information Disclosure Statement dated November 1, 2000 which states in pertinent part:

> "Primaquine, the most important member of the 8-aminoquinoline group, is the only drug which is used in the treatment of relapsing malaria, in spite of its known toxic effects on the host system such as induction of methaemoglobinaemia, haemolytic anaemia in G-6-PD deficient cases and toxicity in pregnant woman. Primaquine and other 8-aminoquinolines, are also known to produce oxidative stress, and inhibit various components of hepatic microsomal mixed function oxidase (MFO) system both *in vivo* and *in vitro*." (References omitted.)

Applicants also call the Examiner's attention to the fact that the need for a solution to the problem exists more than sixty (60) years after issuance of the Andersag patent!

The evidence of record in the specification shows that the claimed method satisfies the long-felt need for a solution to the problem. The evidence shows an enhanced gametocytocidal activity of the claimed compound (see specification at pages 14 - 15 and Tables I - II) and a reduced toxicity in methaemoglobin and glutathione tests (see specification at pages 15 - 16 and Tables IV - VI). This evidence of enhanced effectiveness as compared with "the most important member of the 8-aminoquinoline group" (see Saxena et al excerpt above) not only shows that the claimed method satisfies a long-felt need, but it also shows unexpected results, as next discussed.

Applicants respectfully disagree with the Examiner's contention that the evidence in the specification is not unexpected. The cited art does not disclose any biological activity nor does

it show any improvement in the profile of the biological activity of the amines used. The only disclosure relates to the reaction with therapeutically useful amines. There is no disclosure apart from a general statement on page 1, lines 5 - 8, that the compounds of the cited art are useful for treatment of malarial parasites. Primaquine itself and its toxic metabolites were developed much subsequent to the Andersag Patent. The present specification specifically discloses the problems associated with primaquine and also discloses how the problem of high toxicity is overcome by incorporating an enaminone functionality in the primaquine derivative. As such, this modification to reduce toxicity is unexpected. The reduction of toxicity is unexpected not only over primaquine but also over the cited art.

Andersag's patent relates to condensation products of acetylbutyrolactones and primary amines of the aromatic and heteroaromatic series. The claimed invention is an enaminone derivative of primaquine of the 8-aminoqumoline class wherein toxic activity is reduced. The difference in chemical structure between the closest compound of the cited art and the compound of the claimed invention is significant - the presence of the amino group in the 8-position of its amino functionality bound to a CH_2 group rather than the $CH(CH_3)$ group as in the cited compound would be expected significantly to alter the properties of this amino position. Also, the cited compound has a lactone group with a beta methyl substituent that is not present in the compound of the invention. As such, the differences in structure between the cited compound and the compound of the instant invention are significant. Accordingly, Andersag provides no teaching or guidance or indication that a person skilled in the art would be motivated to modify the compound of Example 11 of Andersag to arrive at the compound of the invention.

In so far as obviousness of the gametocytocidal activity, low toxicity, controlled delivery facilitation, etc. are concerned, neither Andersag nor even the prior art acknowledged in the present specification leads to the teaching in the present specification that putting enaminone at the terminal nitrogen atom will result in the slowing down of chain degradation, reduce methaemoglobin formation thereby lessening toxicity, or show lower toxicity in terms of increased levels of glutathione.

It is respectfully submitted to be incorrect to state that gametocytocidal activity, low toxicity, controlled delivery facilitation, etc., are inherent in the compounds of the art. There is sufficient disclosure in the art and acknowledged in the specification that these properties are not inherent in the class of compounds to which the primaquine derivative of the invention belongs. As is clear from the prior art acknowledged in the specification and from the Saxena et al reference discussed above, high toxicity of primaquine affects its use as an antimalarial agent despite its otherwise demonstrable activity in terms of blood schizontocidal, tissue schizontocidal and gametocytocidal activity. The prior art metabolites of primaquine were either non-functional, or also responsible for its toxicity. The specific art disclosing these problems is already disclosed in the specification. The claimed invention overcomes these problems.

Primaquine is toxic since its oxidative metabolites of both N-alkylated and N-dealkylated origin produce secondary metabolite or o- or p- quinonoide nature after one electron oxidation. However, metabolites with intact side chains are less toxic. The Applicants therefore envisaged putting enaminone at the terminal nitrogen in order to slow down chain

degradation. While the Applicants have not yet generated data on this aspect, literature evidence indicates that the enaminone functionality is resistant to acidic hydrolysis (J. V. Greenhill, Chew. Soc. Rev. 6, 277 (1977)). The reduction of toxicity in terms of methaemoglobin formation does provide evidence of the slowness of the chain degradation as well. Also, as is demonstrated in the specification on page 16, last paragraph, use of primaquine *per se* causes drug induced haemolysis in persons deficient in G-6PD enzyme. The use of the derivative of Formula I of the invention, does not cause this result.

There is no teaching or guidance in Andersag individually or in combination with any other prior art that putting enaminone at the terminal nitrogen atom will lower the levels of oxidation of glutathione and reduce the levels of methaemoglobin formation thereby lessening the toxicity. In fact, Andersag is completely silent on the toxicity of the products described therein.

Also, to Applicants' knowledge, there is no prior art available of any disclosure of the enhanced or unproved gametocytocidal activity of the claimed derivative of Formula I. There is also no prior art disclosure or indication that the properties claimed in claim 11 or disclosed in the specification as being possessed by the claimed derivative of Formula I are inherent chemical and/or physical properties. On the contrary, all prior art teaching indicates that primaquine and its rnetabolites actually are more toxic, and/or that some metabolites are also completely non-functional.

Claim 20 cannot be said to be anticipated or obvious over Andersag since the product

itself is unobvious for reasons discussed above. Morever, the process of the claimed invention results in easy isolation of the product without requiring vacuum distillation and simple crystallization provides a product of high pharmacopoeial standard. The process cannot be said to be obvious over Andersag - the parameters are different, the product is completely different, the field of art is also different.

In view of the above, all claims of record are believed patentably to distinguish over the cited art and the application is believed to be in allowable form. An early Notice of Allowability is earnestly solicited and is believed to be fully warranted.

Respectfully submitted,

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